



Review and Analysis of Industry Documents Regarding Dissolvable Tobacco Products: Health Effects

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Purpose

- Inform recommendations of the Tobacco Product Scientific Advisory Committee (TPSAC) regarding the health effects of dissolvable tobacco products
- Identify industry documents of potential interest to the TPSAC
- ***Disclaimer:*** Although this presentation is being done under contract with the Center for Tobacco Products at FDA, the content and conclusions of the presentation are RTI International's. The information is being provided to TPSAC to aid the committee in its evaluation of the issues and questions referred to the committee.

Topics of Interest

- Topic 4: Health effects of dissolvable tobacco products
- Looked for information regarding:
 - Health warnings
 - Short-term health effects
 - Injury (included in closed session only)
 - Accidental ingestion and child safety concerns

Background

- According to NCI and IARC there is no safe form of tobacco¹⁻²
- At least 28 chemicals in smokeless tobacco have been found to cause cancer¹⁻²
- According to NCI, the most harmful chemicals in smokeless tobacco are tobacco-specific nitrosamines (TSNAs), which are formed during the growing, curing, fermenting, and aging of tobacco¹
- The level of TSNAs varies by product¹
- Scientists have found that the nitrosamine level is directly related to the risk of cancer¹⁻²

Background - continued

- Diseases linked to use of smokeless tobacco¹⁻³ :
 - Cancer
 - Oral
 - Esophageal
 - Pancreatic
 - Heart disease
 - Oral Health
 - Oral lesions including leukoplakia
 - Gum recession and disease
 - Tooth decay
 - Reproductive Health
 - Preeclampsia
 - Premature birth
 - Low birth weight
 - Reduced sperm quantity and quality
 - Nicotine Addiction and Dependence

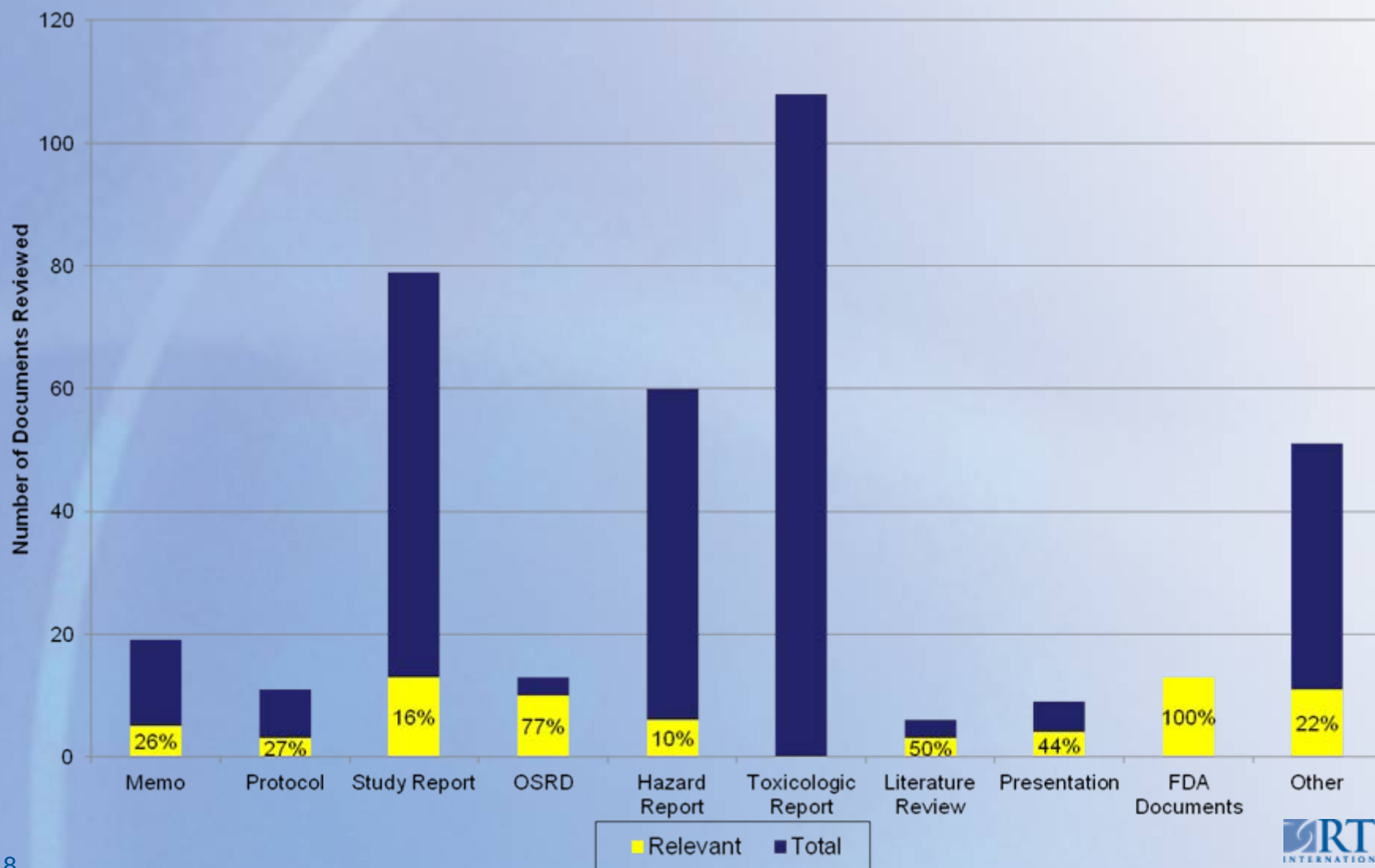
Background - continued

- No epidemiological studies have been performed with dissolvable tobacco products
- Long term effects of dissolvable tobacco product use are unknown

Summary of Documents

- Documents for review identified using 3 methods
 - Used Company designation of “Health Effects”
 - Used search terms “Health” and “Injury”
 - Reviewed document summaries
- A total of 369 documents (20,911 pages) were identified for detailed reviewed by two epidemiologists for relevant information on the health effects of dissolvable tobacco products:
 - Relevant - 68
 - Not relevant - 280
 - Duplicate Bates or information – 21

Types of Documents Reviewed



Types of Documents Reviewed

- Memo
 - Basic science memos
 - E-mails
 - Human research review committee memos
 - Laboratory research memos
 - Product assessment division test memo
 - Product evaluation memos
 - Scientific report memos
- Protocol
 - Clinical study protocols
 - Scientific protocols
- Study Report
 - Clinical reports
 - Laboratory reports
 - Manuscripts

Types of Documents Reviewed - continued

- Other Study Related Documents (OSRD)
 - Confidentiality statements
 - Exit interviews
 - Informed consent
 - Opinion surveys
 - Product brochures
 - Proposals
 - Tables
- Hazard Report
 - Hazard management reports
 - Hazardous substance data bank reports
 - Product hazard analyses
 - Risk assessments

Types of Documents Reviewed - continued

- Toxicologic Report [keyword search for “health” and “injury” identified the following documents warranting review for potential health effects]
 - Commercial product lists
 - FEMA assessments
 - Ingredient lists
 - Material safety data sheet
 - Vendor/food documentation
- Literature Review
 - Frequency and outcomes of accidental ingestion of tobacco products in children
 - Hazardous potential of tobacco product ingredients
 - Nicotine poisoning in children
- Presentation
 - Exit interview results
 - Laboratory research
 - Poster abstract
 - Scientific reports
 - Study design and objectives

Types of Documents Reviewed - continued

- Copies of Documents Provided to FDA
 - Correspondence
 - Modified risk tobacco product applications
 - Submissions pursuant to the Family Smoking Prevention and Tobacco Control Act
- Other
 - Article request forms
 - Market surveys
 - Monographs
 - Notes
 - Pages from Canadian Centre for Occupational Health and Safety and Encyclopedia of Occupational Health and Safety
 - Publication reviews
 - Search requests
 - Summary of commercial requests
 - Tobacco product/process change in management forms

Mandated Health Warnings

The Family Smoking Prevention and Tobacco Control Act – Public Law 111-31, June, 22, 2009 requires that every smokeless tobacco package and advertisement include one of the following warnings:

WARNING: This product can cause mouth cancer.

WARNING : This product can cause gum disease and tooth loss.

WARNING : This product is not a safe alternative to cigarettes.

WARNING : Smokeless tobacco is addictive.

Warning Label Example – Camel Orbs



Short-Term Health Effects – Ariva and Stonewall

- The Company occasionally has received reports primarily from smokers using a smokeless tobacco product for the first time concerning the type of symptoms associated with the oral absorption of nicotine:
 - Burning sensation
 - Hiccups
 - Nausea
- Ariva-BDL, Stonewall-BDL, original Ariva, and original Stonewall are nauseating to the nontolerant user
 - Ariva-BDL and Stonewall-BDL are newer products with levels of TSNAs below detectable limits (BDL)

Short-Term Health Effects - Ariva

- In study by Carpenter and Gray, 2010⁴ most common adverse events reported among smokers who used Ariva along with conventional cigarettes were nausea, hiccups, and insomnia
- Product label message “As with other tobacco products, some users may experience temporary dizziness, heartburn, or nausea.”



Short-Term Health Effects – Dissolvable Tobacco Products

- The following adverse events were reported in Company studies for various dissolvable tobacco products:

- | | |
|---------------------------------------|-------------------------|
| ▪ Indigestion/heartburn/upset stomach | ▪ Tooth/gum sensitivity |
| ▪ Nausea/vomiting | ▪ Dizziness |
| ▪ Increased burping | ▪ Nervousness |
| ▪ Throat discomfort/burn/irritation | ▪ Excess saliva |
| ▪ Coughing | ▪ Dry mouth |
| ▪ Mouth tingle/burn/irritation | ▪ Headache |
| ▪ Tongue irritation | ▪ Increased heart rate |
| ▪ Gum/cheek numbness/burn/irritation | ▪ Hiccups |

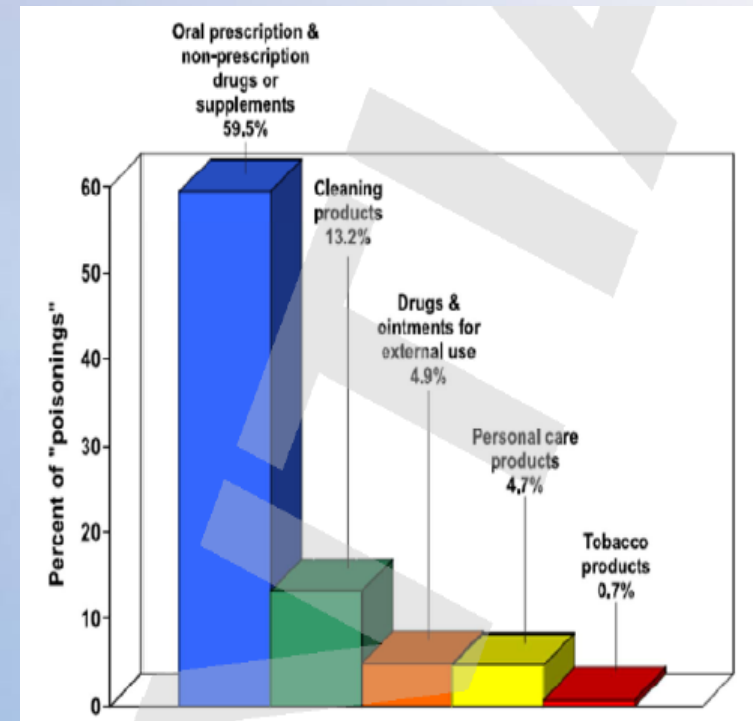
Accidental Poisoning and Child Safety Concerns

- Concerns have recently been raised about smokeless tobacco products and acute toxicity, especially from nicotine, associated with accidental ingestion by young children
- 27 years of annual reports (1983-2009) published by the American Association of Poison Control Centers (AAPCC) were analyzed for occurrence and outcomes associated with accidental ingestion events involving tobacco and pharmaceutical nicotine products among children⁵
 - 0.37% of exposure contacts involved tobacco products; the majority 89% occurred in children <6 years old
 - 5,250 reports of children ingesting subcategory of tobacco products “chewing tobacco or snuff” during 2005-2009; 8 major outcomes (0.1%); No fatalities

Accidental Poisoning and Child Safety Concerns - continued

- Literature search and review conducted related to accidental ingestion of tobacco products among children⁵
- According to surveillance data presented from the NEISS cited from an article by Franklin and Rogers⁶, the estimate of nonfatal poisoning rates for children <5 treated in US hospital emergency departments in 2004 was only 0.7% for ingestion of tobacco products compared with 59.5% for ingestion of oral prescription and non-prescription drug

Estimates of Nonfatal Poisoning Rates For Children <5 Years of Age Treated in US Hospital Emergency Departments (Franklin and Rogers 2008)⁶



Source: US Consumer Product Safety Commission
National Electronic Injury Surveillance System (NEISS)

Accidental Poisoning and Child Safety Concerns – Ariva and Stonewall

- In 10 years of marketing the Company never received a report of serious pediatric toxicity (requiring medical evaluation or treatment). The few reports involved toddlers who obtained the product from a third-party source.
- Review of the entire AAPCC for 2009 - Q1 2010 revealed 527 pediatric “snuff” cases where a product could be identified; 524 involved a moist snuff, one involved Ariva, one involved Stonewall, and one involved an unidentified dissolvable tobacco product.
 - All three pediatric cases had either “no effect” or a “minor effect” and resolved with home care.
 - According to the Company, the recent AAPCC experience does not indicate a significant pediatric risk from Ariva and Stonewall.

Accidental Poisoning and Child Safety Concerns – Ariva and Stonewall

- The Company has done very limited child safety testing, but based on the very few reports of pediatric accidental exposure (fewer than a dozen in nine years in the market place) and the product complaints from adults (the package is not easy for older adults to open) they feel confident that the packaging is adequate to deter younger children
- According to the Company, symptomatic ingestions are possible, but serious toxicity is unlikely. No cases of serious toxicity (pediatric overdose, hospitalizations, injury, or death) involving Ariva (1.5 mg) or Stonewall (4 mg) have been reported to Star



Accidental Poisoning and Child Safety Concerns - Marlboro and Skoal Smokeless Tobacco Sticks

- Accidental Poisoning
 - According to the Company, the incidence and severity of accidental poisoning is very low for smokeless tobacco products.
 - Ingestion of these products poses no more risk than commonly encountered from other available smokeless tobacco products

References

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